Roger Citron, RPh, RPh
Montana Dept. of Public Health & Services
1400 Broadway
P.O. Box 202951
Helena, MT 59620-2951

Boehringer Ingelheim Pharmaceuticals, Inc.

April 10, 2007

DRUG INFORMATION

Dear Mr. Citron, RPh:

900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368
Telephone (800) 542-6257
Telefax (800) 821-7119

Thank you for discussing SPIRIVA® HandiHaler® (tiotropium bromide inhalation powder) with your Boehringer Ingelheim Pharmaceuticals, Area Manager, Managed Care, Gary Brungardt. You requested information regarding the following topic(s):

Hyperinflation
Exercise Tolerance
Formoterol versus and in Combination with SPIRIVA
Salmeterol Plus Fluticasone Combined with SPIRIVA
Salmeterol Plus Fluticasone versus SPIRIVA
Exacerbation Reduction

SPIRIVA HandiHaler is indicated for the long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. Any other use not included in the package insert(s) is an investigational use and cannot be recommended by Boehringer Ingelheim Pharmaceuticals, Inc.

Thank you for your interest in SPIRIVA HandiHaler. If you should have any further questions, please do not hesitate to contact the Drug Information Unit.

Sincerely,

Barbara Payne, Pharm.D.

Barbara Ann Payne, Pharm.D., R.Ph.
Manager, Medical Information
Drug Information Unit
druginfo@rdg.boehringer-ingelheim.com
BLAPIERRE/2007-008171

Hyperinflation

Hyperinflation, which occurs at rest and worsens with exercise, is a physiological abnormality that is commonly seen in patients with chronic obstructive pulmonary disease (COPD). It is manifested primarily by an increase in functional residual capacity (FRC) and a decrease in inspiratory capacity (IC). This condition can lead to restrictions in tidal volume expansion during activity and also places the muscles of respiration at a mechanical disadvantage. Hyperinflation increases the work of breathing, worsens with exercise, and therefore reduces exercise tolerance (dynamic hyperinflation). Inhaled bronchodilators improve dynamic hyperinflation, as well as hyperinflation at rest (static hyperinflation), thereby reducing the work of breathing and increasing exercise tolerance.[1]

Numerous clinical studies and reviews have shown an improvement in the reduction of hyperinflation with the use of inhaled tiotropium (*Spiriva*®) in patients with chronic obstructive pulmonary disease (COPD).[2-7]

Celli et al. evaluated the effect of *Spiriva*® 18mcg daily on inspiratory capacity (IC) in a 4-week, randomized, double-blind, placebo-controlled study conducted in 81 patients with stable COPD. The mean age of the subjects was 63 years old, 62% were men, and mean baseline forced expiratory volume in 1 second (FEV_1) was 1.12L (43% of predicted). At each of the visits (weeks 0, 2 and 4) FEV_1, forced volume capacity (FVC), IC, slow vital capacity (SVC), and thoracic gas volume (TGV) or functional residual capacity (FRC) were measured prior to study drug (-60min and -15min) and after study drug (30 min, 60 min, 120 min, and 180 min). The percentage improvement in area under the curve above baseline with *Spiriva*® was similar among FEV_1 and lung volumes (FEV_1 18%; FVC 20%; SVC 16%; IC 16%; FRC 14%). Observed improvements in IC and reductions in TGV or FRC with once daily *Spiriva*® reflect improvements in hyperinflation that are maintained over 24 hours.[2]

In a 12-week multicenter, randomized, double-blind comparison of once-daily inhaled *Spiriva*® (N=46) with placebo (N= 54), *Spiriva*® showed significant decrease in lung hyperinflation as measured by forced volume capacity (FVC), inspiratory capacity (IC), and slow vital capacity (SVC). The improvement in both spirometric measurements, FVC (trough and peak) and IC (trough and peak) can be shown on figure 1 and figure 2, respectively. Compared to placebo, *Spiriva*® has induced greater improvement in the peak SVC. In addition, airway obstruction was also improved in the *Spiriva*® group, compared to the placebo group. This was demonstrated by significant improvements in Forced Expiratory Volume in the first second (FEV1) and peak expiratory flow rate (PEFR) [$p < 0.05$, respectively for all measures]. In addition, *Spiriva*® provided a measurable improvement in exercise capacity and dyspnea. At the end of the trial, patients in the *Spiriva*® group had a consistent and clinically significant improvement in their health-related quality of life (HRQoL), which was measured by the St. George's Respiratory Questionnaire (SGRQ) total score ($p < 0.05$ vs placebo).[3]

Figure 1: Mean trough (a**,** predose) and peak (b, postdose) FVC. Adjusted means (± 2 SE) are shown (* $p < 0.05$, ** $p < 0.001$ vs. placebo).[3]

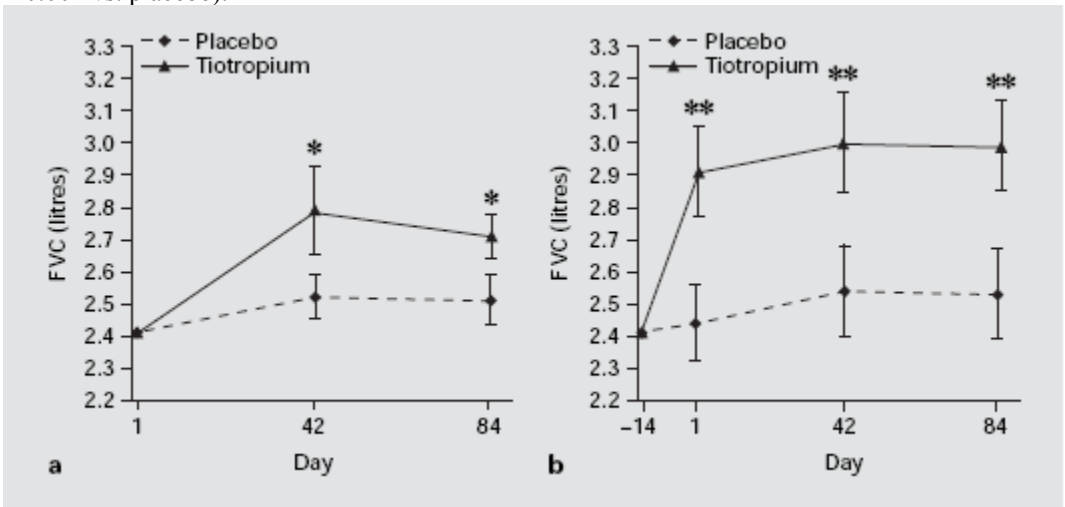
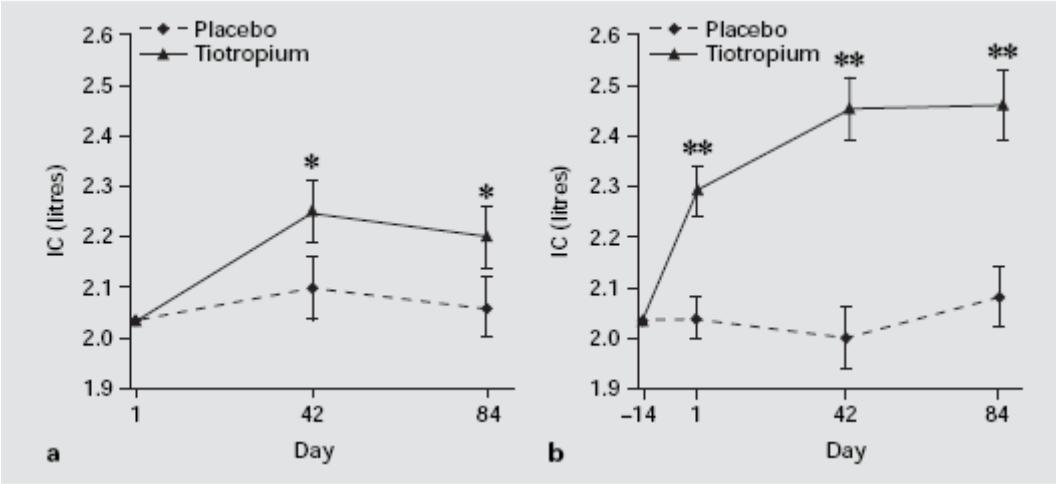


Figure 2: Mean trough (a**,** predose) and peak (b, postdose) IC. Adjusted means (± 2 SE) are shown (* p <0.05, ** p < 0.001 vs. placebo). [3]



A review article by Copper described how hyperinflation of the lungs reduces IC, not only at rest (static hyperinflation) but also during physical activity (dynamic hyperinflation). The article also reviewed the evidence on the effects of bronchodilators (such as *Spiriva*®) on hyperinflation, exercise endurance, and dyspnea in patients with chronic obstructive pulmonary disease (COPD).[4] The data on *Spiriva*® are summarized in table 1. The author concluded that bronchodilators such as *Spiriva*® can reduce airway resistance and ventilatory requirements during exercise. These changes can lead to an improvement in IC, which is indicative of reduced hyperinflation. Also, the improvement in IC was associated with a significant reduction in dyspnea and increased exercise tolerance.

Table1[4]:

Bronchodilator	Study	Year	N	Baseline FEV1 (%)	Increase in Static IC* (mL)	Increase in Dynamic IC† (mL)	Increase in Exercise Endurance	Change in Dyspnea	*P* Value
Spiriva®	Celli et al[2]	2003	81	43	350	NM	NM	NM	<0.01 vs. placebo
	O'Donnell et al[5]	2004	187	44	230	180	105 sec	↓II	<0.05 vs. placebo
	Maltais et al[6]	2005	261	43	220 150	220 140	235 sec 171 sec	↓II ↓II	<0.01 vs. placebo¶ <0.01 vs. placebo#

FEV_1 =forced expiratory volume in 1 second; IC = inspiratory capacity; NM = not measured
*IC measured during body plethysmography as total lung capacity (TLC) minus functional residual capacity.
†IC measured at isotime during constant load submaximal exercise.
II Dyspnea reduced at isotime.
¶ Measured 8 hours after dosing.
# Measured 2.25 hours after dosing.

Another review article by Casaburi discussed several interventions that can reduce hyperinflation during exercise. These interventions are bronchodilator therapy, inhalation of supplemental oxygen or a helium/oxygen mixture, and rehabilitative exercise programs. The article suggested that the combinations of rehabilitative exercise training with supplemental oxygen, or with *Spiriva*®, have been found to yield additive effects on reducing dynamic hyperinflation and that subsequently can improve the mobility of COPD patients.[7]

References:

1. ER Sutherland, RM Cherniack. Management of chronic obstructive pulmonary disease -current concepts. *NEJM* 2004; 350: 2689-97.

2. B Celli, R ZuWallack, S Wang, et al. Improvement in resting inspiratory capacity and hyperinflation with tiotropium in chronic obstructive pulmonary disease patients with increased static lung volumes. *Chest* 2003;124:1743–1748.

3. C Verkindre, F Bart, B Aguilaniu et al. The effect of tiotropium on hyperinflation and exercise capacity in chronic obstructive pulmonary disease. *Respiration* 2006; 73:420-427.

4. CB Cooper**.** The connection between chronic obstructive pulmonary disease symptoms and hyperinflation and its impact on exercise and function. *The American Journal of Medicine* 2006; 119 (10) Suppl1: 21-31.

5. DE O'Donnell DE, T Fluge , F Gerken , et al. Effects of tiotropium on lung hyperinflation, dyspnea and exercise tolerance in patients with chronic obstructive pulmonary disease. *Eur Respir J* 2004;23:832–840.

6. Maltais F, Hamilton A, Marciniuk D, et al. Improvements in symptoms limited exercise performance over 8 h with once-daily tiotropium in patients with chronic obstructive pulmonary disease. *Chest* 2005;128:1168 –1178.

7. R Casaburi, J Porszasz. Reduction of hyperinflation by pharmacologic and other interventions**.** *Proc Am Thorac Soc* 2006; 3:185-189.

Exercise Tolerance

Exercise tolerance is one of the important clinical outcomes in evaluating chronic obstructive pulmonary disease (COPD) patients.[1] Numerous clinical studies and reviews have shown an improvement in exercise tolerance with the use of inhaled tiotropium (*Spiriva*®) in COPD. [1-7]

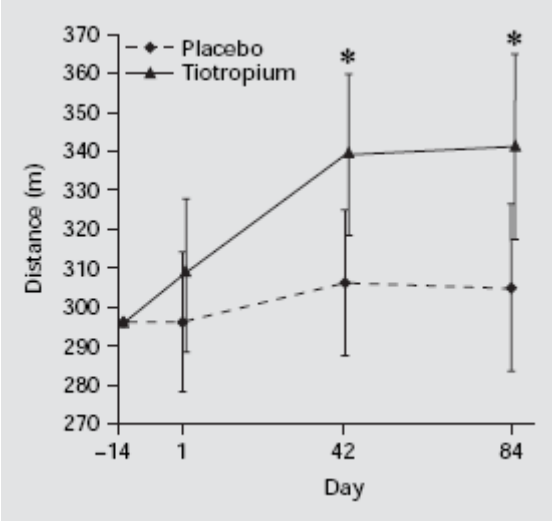
The effects of *Spiriva*® on exercise tolerance were evaluated in a six-week, randomized, placebo-controlled, parallel-group study involving 187 patients with mild-to-severe COPD with static hyperinflation. Exertional dyspnea, dynamic lung hyperinflation, and static lung volumes (trapped air volume, residual volume, and functional residual capacity) were evaluated as secondary endpoints. Patients received either *Spiriva*® 18 µg once daily (n = 96) or placebo (n = 91) with exercise tolerance (measured by endurance time during constant work rate cycle ergometry) performed on test days -10, -5, 0, 21, and 42 at 135 minutes after study drug administration. An incremental exercise test was performed at day –15. Day –10 was considered a practice test. Pretreatment baseline was at day –5. Lung volumes were assessed by body plethysmograph and dyspnea was measured by the baseline and transition dyspnea indexes. At baseline, average endurance time for all patients measured 8.2 minutes. After three weeks of treatment, *Spiriva*® patients exercised 1.1 minutes longer than those taking placebo ($p<0.0395$). At six weeks, patients taking *Spiriva*® could exercise an additional 1.7 minutes compared to patients taking placebo, representing a 21.4 percent improvement ($p < 0.0099$). In addition, patients in the *Spiriva*® group experienced an improvement in lung volume, lung function, and dyspnea.[2]

A second international exercise trial of 261 patients has recently been completed. The trial confirmed the pattern of responses observed in the first trial. *Spiriva*® improved airflow, reduced hyperinflation at rest and during exercise, reduced exertional dyspnea and improved symptom-limited exercise tolerance. At 6 weeks endurance time had improved by a mean of 44% (236 seconds) relative to placebo ($p<0.01$). There were two patients who had profoundly prolonged endurance times with *Spiriva*®. The removal of these two patients still resulted in a mean increase of 31% (164 seconds) relative to placebo ($p<0.01$). Furthermore, this study shows that this improvement is present at 2.25 hours and at 8 hours after dosing after 6 weeks of treatment. Median increases in exercise tolerance at 2.25 hours after dosing on day 42 (compared to the baseline exercise tolerance on day -5) were 110 seconds in the tiotropium group compared to 10 seconds in the placebo group ($p=0.003$). In summary, *Spiriva*® significantly improved exercise

tolerance following three and six weeks of treatment. The exercise trials illustrate the benefits of *Spiriva*® as well as providing a pathophysiologic explanation for these benefits. *Spiriva*® improves airflow and reduces hyperinflation thereby permitting patients to increase their ventilation with less breathlessness and, as a result, increase their ability to engage in physical activities longer and more comfortably. [3]

In a 12-week multicenter, randomized, double-blind comparison of once-daily inhaled *Spiriva*® (N=46) with placebo (N= 54), *Spiriva*® showed significant decrease in lung hyperinflation as measured by forced volume capacity (FVC), inspiratory capacity (IC), and slow vital capacity (SVC). Also and as shown in figure 1, treatment with *Spiriva*® resulted in significantly improved exercise capacity in the shuttle walking test (SWT). *Spiriva*®, compared with placebo, provided a measurable improvement in dyspnea as measured by the transition dyspnea index (TDI) score. At the end of the trial, patients in the *Spiriva*® group had a consistent and clinically significant improvement in their health-related quality of life (HRQoL), which was measured by the St. George's Respiratory Questionnaire (SGRQ) total score ($p < 0.05$ vs placebo).[1]

Figure 1: SWT (postdose). Adjusted means (± 2 SE) are shown (* $p < 0.05$ vs. placebo) [1].



A review article by Copper reviewed the evidence on the effects of bronchodilators (such as *Spiriva*®) on exercise endurance, hyperinflation, and dyspnea in patients with chronic obstructive pulmonary disease (COPD). The data on *Spiriva*® are summarized in table 1. The author concluded that bronchodilators such as *Spiriva*® can reduce airway resistance and ventilatory requirements during exercise. These changes can lead to an improvement in IC, which is indicative of reduced hyperinflation. Also, the improvement in IC was associated with a significant reduction in dyspnea and increased exercise tolerance. [4]

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*IC measured during body plethysmography as total lung capacity (TLC) minus functional residual capacity.
†IC measured at isotime during constant load submaximal exercise.
II Dyspnea reduced at isotime.
¶ Measured 8 hours after dosing.
# Measured 2.25 hours after dosing.

The Effect on Exercise Tolerance with the Combination of *Spiriva*® and Pulmonary Rehabilitation:

A recent study by Casaburi et al. showed an improvement in exercise tolerance with the combination of *Spiriva*® and pulmonary rehabilitation in patients with COPD. The hypothesis was that ventilatory mechanics improvements from *Spiriva*® would permit enhanced ability to train muscles of ambulation and therefore augment exercise tolerance benefits of pulmonary rehabilitation. In a randomized double blind, placebo-controlled trial (*Spiriva*®, n=47; placebo, n=44), *Spiriva*® 18mcg daily was administered to COPD patients participating in 8 weeks of pulmonary rehabilitation (treadmill training three times a week; ≥ 30 minutes per session) at 17 sites. Study drug was administered 5 weeks prior to, 8 weeks during, and 12 weeks following pulmonary rehabilitation. The primary end point was treadmill walking (0% incline) endurance time at 80% of maximum speed attained in an initial incremental test. The transition dyspnea index (TDI), St. George's respiratory questionnaire (SGRQ), and rescue albuterol use were secondary end points. The mean age of the 93 participants was 67 years, 57% were men, and mean FEV_1 was 0.88L (34% of predicted). [6]

The mean endurance time difference (*Spiriva*® minus placebo) prior to pulmonary rehabilitation, at the end of pulmonary rehabilitation, and 12 weeks after pulmonary rehabilitation were 1.65 minutes (p=0.183), 5.35 minutes (p=0.025), and 6.60 minutes (p=0.018), respectively. Mean TDI focal scores at the end of pulmonary rehabilitation were 1.75 for *Spiriva*® and 0.91 for placebo (p>0.05). At 12 weeks after pulmonary rehabilitation, TDI focal scores were 1.75 for *Spiriva*® and 0.08 for placebo (p<0.05). Relative to placebo, *Spiriva*® improved SGRQ total scores by 3.86 at the end of pulmonary rehabilitation and 4.44 at 12 weeks after pulmonary rehabilitation (p>0.05). Mean albuterol use declined following pulmonary rehabilitation plus *Spiriva*®, compared to pulmonary rehabilitation alone (p≤0.05 for 17 of 25 weeks). In conclusion, *Spiriva*® in combination with pulmonary rehabilitation improved endurance of a constant work rate treadmill task and produced clinically meaningful improvements in dyspnea and health status compared to pulmonary rehabilitation alone. Improvements with *Spiriva*® were sustained for 3 months following completion of pulmonary rehabilitation. [6]

A review article by same author discussed several interventions that can reduce hyperinflation during exercise. These interventions are bronchodilator therapy, inhalation of supplemental oxygen or a helium/oxygen mixture, and rehabilitative exercise programs. The article suggested that the combinations of rehabilitative exercise training with supplemental oxygen, or with *Spiriva*®, have been found to yield additive effects on reducing dynamic hyperinflation and subsequently can improve the mobility and exercise tolerance in COPD patients.[7]

References:

1. C Verkindre, F Bart, B Aguilaniu et al. The effect of tiotropium on hyperinflation and exercise capacity in chronic obstructive pulmonary disease. *Respiration* 2006; 73:420-427.

2. DE O'Donnell DE, T Fluge , F Gerken , et al. Effects of tiotropium on lung hyperinflation, dyspnea and exercise tolerance in patients with chronic obstructive pulmonary disease. *Eur Respir J* 2004;23:832–840.

3. Maltais F, Hamilton A, Marciniuk D, et al. Improvements in symptoms limited exercise performance over 8 h with once-daily tiotropium in patients with chronic obstructive pulmonary disease. *Chest* 2005;128:1168 –1178.

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5. B Celli, R ZuWallack, S Wang, et al. Improvement in resting inspiratory capacity and hyperinflation with tiotropium in chronic obstructive pulmonary disease patients with increased static lung volumes. *Chest* 2003;124:1743–1748.

6. R Casaburi, D Kukafka, CB Cooper, et al. Improvement in exercise tolerance with the combination of tiotropium and pulmonary rehabilitation in patients with chronic obstructive pulmonary disease. *Chest* 2005;127:809–817.

7. R Casaburi, J Porszasz. Reduction of hyperinflation by pharmacologic and other interventions**.** *Proc Am Thorac Soc* 2006; 3:185-189.

Formoterol versus and in Combination with SPIRIVA

The Global Initiative for Obstructive Lung Disease (GOLD) Guidelines Update of 2005 recommends the use of regular treatment with long-acting bronchodilators, including tiotropium, rather than short-acting bronchodilators for moderate to very severe COPD. For patients not sufficiently controlled on monotherapy, GOLD Guidelines and ATS/ERS Guidelines recommend combination therapy, as with an inhaled anticholinergic and a beta 2 adrenoceptor agonist.

Studies have suggested that the once-daily anticholinergic tiotropium may be considered the bronchodilator of choice for the maintenance therapy of COPD. Cazzola et al [1] designed a double-blind, double-dummy, cross-over, randomized pilot study to compare the acute bronchodilator efficacy of a single dose of formoterol 12mcg with that of tiotropium 18mcg in 20 patients with stable COPD. The acute effects of adding tiotropium 18mcg to formoterol 12mcg were explored in this study to determine the potential for additive bronchodilation. Serial measurements of FEV_1 were performed over 24 hours. Formoterol, alone or in combination with tiotropium, produced a significantly faster onset of action and showed a trend for a greater maximum bronchodilation than tiotropium alone. At 24 hours, mean FEV_1 continued to be significantly higher than pre-dosing value following tiotropium and formoterol + tiotropium. However, the study is limited as additional bronchodilator effects with tiotropium occur beyond the first dose with pharmacodynamic steady state being attained within eight days. Single dose studies for maintenance treatment need to be interpreted with caution.

Once daily tiotropium 18mcg inhaled via the HandiHaler, twice daily formoterol 12mcg inhaled as dry powder, and the once daily free combination of both drugs (tiotropium + formoterol) were compared by van Noord et al.[2] using a 3-way, double-blind, crossover design of 6-week treatment periods. Mean baseline FEV_1 of the 74 randomized patients was 1.05L (32% of predicted), mean age was 64.8 years. Bronchodilator efficacy (FEV_1, FVC) was assessed at the end of each 6-week treatment period for a 24-hour observation period. Tiotropium was superior to formoterol during the day for FEV_1 and FVC average (0-12hours) as well as trough response; no difference was observed in FEV_1 and FVC average (12-24 hours). The free combination of both drugs taken once daily appeared to be superior to the single drugs for most of the endpoints, except for FEV_1 and FVC trough response, and average FVC (12-24 hours) in COPD patients with moderate to severe airflow obstruction.

A combination of two bronchodilators from different classes can provide additive effects, and a study was designed by Rabe KF et al.[3] to evaluate the short-term merits of two different combination options. A 6-week, multicenter, randomized, double-blind, parallel group study was conducted to compare efficacy and safety of tiotopium 18mcg once daily *plus* formoterol 12mcg twice daily to salmeterol 50mcg twice daily *plus* fluticasone 500mcg twice daily in COPD patients. After 6 weeks of treatment, a 12-hour profile of pulmonary function testings (FEV_1, FVC) was obtained. Co-primary endpoints were FEV_1 area under the curve for 0 to 12 hours (FEV_1 AUC_{0-12}) and peak FEV_1. Efficacy evaluation (intent-to-treat) comprised 592 patients [tiotropium + formoterol: n=297, salmeterol + fluticasone: n=295]. Baseline characteristics of the two groups were comparable [mean baseline FEV_1: 1.32L, age: 62.1 yrs, FEV_1 % predicted: 45.6%]. Tiotropium + formoterol was significantly superior in FEV_1 AUC_{0-12} (78mL, p=0.0006) and peak FEV_1 (103mL, $p<0.0001$) to salmeterol + fluticasone. At each timepoint (post-dose) for FEV_1 and FVC, tiotropium + formoterol was significantly superior to salmeterol + fluticason ($p<0.05$). Subgroup analysis by severity and reversibility confirmed the overall results. Both treatments were well-tolerated. In this short-term study, tiotropium + formoterol was superior in lung function compared to salmeterol + fluticasone in moderate COPD.

Futher long-term studies are needed to evaluate combination therapies as to their effects on symptoms and exacerbation frequencies.

A randomized, three-way crossover, open-label, placebo-controlled study was conducted by van Noord et al.[4] comparing 2 week treatment periods of tiotropium alone, tiotropium plus formoterol once or twice a day after a 2 week pretreatment period of tiotropium. Ninety-five patients with stable COPD participated. FEV_1, FVC, and resting inpiratory capacity (IC) was measured serially over 24 hours at baseline and after each 2 week period. Circadian variations in these parameters were present at baseline and maintained throughout each treatment period. The mean baseline FEV_1 was 1.05L (38% of predicted). The average improvement in FEV_1 from 0 to 24 hours was 0.8L for tiotropium, 0.16L for tiotropium plus formoterol once daily, and 0.2L for tiotropium plus formoterol twice daily ($p<0.01$ for all values). FEV_1, FVC, and IC improved for longer than 12 hours with add-on formoterol in the morning. Adding a second dose of formoterol produced greater improvement in FEV_1 over the next 12 hours but FVC and IC did not improved less than 12 hours. The addition of formoterol once and twice daily significantly reduced the use of rescue salbutamol during the day and the add-on twice daily also during the evening compared to tiotropium alone. All treatments were well tolerated. The authors conclude that adding formoterol once or twice daily to once daily tiotropium results in improvement in airflow obstruction, resting hyperinflation, and the use of rescue salbutamol.[4]

There have been a limited number of small studies of the addition of SPIRIVA to a long-acting beta-agonist. However, there is extensive clinical experience with concomitant use of anticholinergics and long-acting beta-agonists. Safety concerns are not anticipated when adding SPIRIVA to a long-acting beta-agonist.

1. Cazzola M, Marco F di, Santus P, et al. The Pharmacodynamic effects of single inhaled doses of formoterol, tiotropium and their combination in patients with COPD. *Pulm Pharmacol Ther* 2004;17(1):35-39.

2. van Noord JA, Aumann J, Janssens E, et al. Comparison of once daily tiotropium, twice daily formoterol and the free combination, once daily, in patients with COPD. *Am J Respir Crit Care Med* 2003;167(7):A320

3. Rabe KF, Timmer W, Sagriotis A, Viel K. Comparison of a combination of tiotropium and formoterol to salmeterol and fluticasone in moderate COPD. Ann Cong of the European Respiratory Society, 17-21 September 2005, Copenhagen.

4. van Noord JA, Aumann JL, Janssens E, et al. Effects of tiotropium with and without formoterol on airflow obstruction and resting hyperinflation in patients with COPD. Chest 2006;129(3):509-517.

Salmeterol Plus Fluticasone Combined with SPIRIVA

A recent publication in the Annals of Internal Medicine reviewed the results of the Canadian OPTIMAL trial where the combination of tiotropium with salmeterol or fluticasone-salmeterol was compared to tiotropium alone in improving moderate to severe COPD. The study by Aaron SD et al. was a randomized, double-blind, placebo-controlled trial conducted from Oct 2003 to January 2006 at 27 academic and community medical centers in Canada. 449 patients with moderate to severe COPD participated receiving 1year of treatment with tiotropium with placebo, tiotropium with salmeterol, or tiotropium with fluticasone-salmeterol. The primary endpoint was the proportion of patients who experience a COPD exacerbation that required treatment with systemic steroids or antibiotics.

The proportion of patients in the tiotropium plus placebo group who experienced an exacerbation (62.8%) did not differ from that in the tiotropium plus salmeterol group (64.8%; difference, -2 percentage points[95% CI, -12.8 to 8.8 percentage points] or the tiotropiumplus fluticasone-salmeterol group (60.0%; difference, 2.8 percentage points [CI, -8.2 to13.8 percentage points]. In sensitivity analyses, the point estimates and 95% confidence bounds shifted in the direction favoring tiotropium plus salmeterol and tiotropium plus fluticasone-salmeterol. Tiotropium plus fluticasone-salmeterol improved lung function ($p=0.049$) and disease-specific quality of life ($p=0.01$) and reduced the number of hospitalizations for COPD exacerbations and all-cause hospitalizations compared with tiotropium plus placebo. In contrast, tiotropium plus salmeterol did not statistically improve lung function or hospitalization rates compared with tiotropium plus placebo.

A limitation of the study was that more than 40% of patients who received tiotropium plus placebo and tiotropium plus salmeterol discontinued therapy prematurely, and many crossed over to treatment with open-label inhaled steroids or long-acting beta-agonists.

Adding fluticasone-salmeterol to tiotropium therapy did not statistically influence the rate of COPD exacerbation but did improve lung function, quality of life, and hospitalization rates in patients with moderate to severe COPD.

Salmeterol Plus Fluticasone versus SPIRIVA

A six-week, multicenter, randomized, double-blind, triple-dummy, parallel-group pilot study was conducted to evaluate the spirometric effect size of tiotropium 18mcg daily compared to salmeterol 50mcg twice daily plus fluticasone 250 mcg twice daily in chronic obstructive pulmonary disease (COPD) patients. After 6 weeks of treatment, a 12-hour profile of pulmonary function tests (FEV_1, FVC) was performed. A total of 107 patients were randomized (tiotropium = 56 , salmeterol+fluticasone = 51). Randomization failed to provide treatment groups with comparable baseline characteristics (baseline FEV_1: tiotropium 1.31L [n=56], salmeterol + fluticasone 1.47L [n=51]; reversibility (FEV_1 increase of 12% over baseline and 200mL; tiotropium 55.4%, salmeterol + fluticasone 64.7% of subjects). Mean ages (years): tiotropium (62.4); salmeterol + fluticasone (62.5). The primary endpoint was forced expiratory volume area under curve for time period 0 to 12 hours (FEV_1 AUC_{0-12}) at Day 43.

FEV_1 AUC_{0-12} was 1.55±0.03 L in tiotropium and 1.57±0.04 L in salmeterol + fluticasone (95% CI -0.12, 0.07; p=ns; ITT population). Peak FEV_1 was comparable between tiotropium (1.68±0.04 L) and salmeterol + fluticasone (1.66±0.04 L). Trough FEV_1, although numerically higher in salmeterol + fluticasone, was not significantly different [salmeterol + fluticasone: 1.54±0.03 L; tiotropium: 1.46±0.03 L; 95% CI -0.17, 0.01; p=0.07]. FVC AUC_{0-12} was similar in both arms. Peak FVC and trough FVC were non-significant between groups (peak FVC: salmeterol + fluticasone [3.26±0.07 L]; tiotropium [3.30±0.06 L], p=ns; trough FVC: salmeterol + fluticasone [2.97±0.05 L]; tiotropium [2.93±0.05 L], p=ns). Rescue salbutamol use was similar and both treatments were well tolerated. In this underpowered pilot study, in spite of baseline differences between groups favoring salmeterol + fluticasone, tiotropium and salmeterol + fluticasone demonstrated similar efficacy and spirometric profiles over 12 hours in COPD. (data on file and E Bateman, et al. Ann Cong of the European Respiratory Society, 17-21 September 2005, Copenhagen.)

Exacerbation Reduction

COPD exacerbations and associated hospitalizations are associated with significant morbidity, mortality, health resources utilization and cost. Studies have shown a strong association between hospitalization for COPD exacerbations and mortality.[1-3] Recent data suggests an association between the frequency of exacerbations and the rate of decline in FEV_1 in patients with COPD.[4,5] The phase III trials evaluated exacerbations and exacerbation-related hospitalizations, with exacerbation data captured by the reporting of adverse events. In these core clinical trials COPD exacerbation was defined as a complex of 2 or more new or increased respiratory symptoms (including dyspnea, wheeze, cough, sputum production) lasting at least 3 days and reported as an adverse event. It should be noted that although this definition does not require a treatment intervention, approximately 90% of events reported as exacerbations were treated with antibiotics, systemic corticosteroids or both.

a. 1-Year Trials: SPIRIVA vs. Placebo

As summarized in the table below, SPIRIVA was associated with significantly lower rates of exacerbations and hospitalizations, compared to placebo despite use of concurrent respiratory medications such as albuterol, inhaled steroids and theophyllines as previously prescribed by their physicians and rescue albuterol (provided to all patients).[6] In addition, the percentage of patients using oral steroid medication for COPD exacerbations, was lower with SPIRIVA compared to placebo.[7] In these trials a total of 90 of 550 (16.4%) patients in the SPIRIVA group took oral

steroid bursts for the control of COPD exacerbations compared to 92 of 371 (24.8%) patients in the placebo group over the 49-week treatment period. The difference between the two treatment groups was statistically significant ($p<0.01$).[8]

Exacerbations and Hospitalizations Due to Exacerbations Over 1 Year: SPIRIVA vs. Placebo[6]

	Incidence of Exacerbations*	**Number of Exacerbations per Year†**	**Incidence of Hospitalizations‡**	**Number of Hospitalizations per Year†**
SPIRIVA	36%§	0.76§	5.5%§	0.09§
Placebo	42%	0.95	9.4%	0.16

* Percentage of patients experiencing ≥1 exacerbation during the 1-year study.
† Number of exacerbations/hospitalizations per patient-year.
‡ Percentage of patients experiencing ≥1 hospitalization during the 1-year study.
§ $p<0.05$ vs. placebo.

b. 1-Year Trials: SPIRIVA vs. Ipratropium

SPIRIVA was associated with significant reductions in the incidence and number of exacerbations compared to ipratriopium.[9] SPIRIVA was also associated with a trend towards a lower incidence and frequency of hospitalizations and number of hospitalizations for exacerbations, although these differences did not reach statistical significance. The percentage of patients using oral steroid medication was lower with SPIRIVA compared to ipratropium.[7] In these trials a total of 78 of 356 (21.9%) patients in the SPIRIVA group took oral steroid bursts compared to 50 of 179 (27.9%) patients in the ipratropium group for the control of COPD exacerbations over the 52-week treatment period. The difference between the 2 treatment groups was not statistically significant ($p=0.133$). [8]

Exacerbations and Hospitalizations Due to Exacerbations Over 1 Year: SPIRIVA vs. Ipratropium[9]

	Incidence of Exacerbations*	**Number of Exacerbations per Year†**	**Incidence of Hospitalizations‡**	**Number of Hospitalizations per Year†**
SPIRIVA	35%§	0.73§	7.3%	0.10§§
Ipratropium	46%	0.96	11.7%	0.16

*Percentage of patients experiencing ≥1 exacerbation during the 1-year study.
† Number of exacerbations/hospitalizations per patient-year.
‡ Percentage of patients experiencing ≥1 hospitalization during the 1-year study.
§ $p<0.05$ vs. ipratropium.
§§ $p=0.09$ vs. ipratropium.

c. 6-Month Trials: SPIRIVA vs. Salmeterol vs. Placebo

SPIRIVA significantly reduced exacerbation frequency compared to placebo ($p<0.05$), whereas salmeterol did not. As displayed in the table below, there were trends toward fewer hospitalizations due to exacerbations with SPIRIVA compared to salmeterol and placebo.[10] In these trials, the percentages of patients using oral steroid bursts for exacerbation treatment were 11.2% (SPIRIVA), 13.8% (salmeterol), and 14.5% (placebo), with no significant differences among the treatment groups.[10]

Mean Incidence of Exacerbations and Hospitalizations Due to Exacerbations Over 6 Months: SPIRIVA vs. Salmeterol vs. Placebo[10]

	Incidence of Exacerbations*	**Number of Exacerbations per Year†**	**Incidence of Hospitalizations‡**	**Number of Hospitalizations per Year†**
SPIRIVA	32%§	1.07§	3%	0.10§
Salmeterol	35%	1.23	5%	0.17
Placebo	39%	1.49	5%	0.15

*Percentage of patients experiencing ≥1 exacerbation/hospitalization during the 6-month study.
† Number of exacerbations/hospitalizations per patient-year.
‡ Percentage of patients experiencing ≥1 hospitalization during the 6-month study.
§ $p < 0.05$ vs. placebo.

d. COPD Exacerbation and Hospitalization Study

Design/Objectives

The principal objective of the study was to prospectively confirm the previous observations of decreased frequency of exacerbations and related hospitalizations with SPIRIVA in the one year pivotal trials. This trial was a 6-month, randomized, double-blind, placebo-controlled, parallel group trial in patients with COPD in the Veterans Affairs (VA) Medical System. The trial was conducted at 26 VA Medical Centers in the United States. In accordance with intent to treat (ITT) principles, patients were encouraged to continue study participation for the entire six month observation period even if trial medication was prematurely discontinued.[11]

Patient Demographics/Treatments

A total of 1,829 patients were randomized into the study. The inclusion/exclusion criteria were less restrictive compared to the pivotal trials in order to allow for inclusion of a broader population of patients with COPD including 29% of patients using home oxygen at entry into the study. During the treatment period, patients were permitted to continue using all of their usual respiratory medications (including LABAs) with the single exception of anticholinergic agents. Treatment groups were randomized to receive SPIRIVA 18µg or identical placebo once daily via the HandiHaler.[11]

Assessments

The incidence and frequency of exacerbations of COPD and hospitalizations for exacerbations were assessed. Health resource utilization, including use of antibiotics and steroids for exacerbations, as well as unscheduled outpatient visits were also evaluated. COPD exacerbations in this study were defined by the presence of two or more respiratory symptoms (increased or new onset) with a duration of at least 3 days, and requiring treatment with antibiotics, steroids or hospitalization. [11]

Results

Baseline demographics are provided in the table below.
The study cohort was predominantly male with a mean age of approximately 68 years. The mean FEV_1 was approximately 1.05L (35.6% of predicted normal), consistent with a population of patients with moderate to severe COPD.

Patient Demographics for Exacerbations Study[11]	**SPIRIVA 18µg qd**	**Placebo ***
Randomized (n)	914	915
Age (years, mean)	67.6	68.1
% less than Age 65 years	34.8	30.6
Gender (%)		
Male	98.2	98.8
Female	1.8	1.2
Mean Baseline FEV_1 (L)	1.04	1.04
Mean FEV_1 % predicted	35.6	35.6
FEV_1/FVC (%)	47.9	47.7

***** All randomized patients were provided with albuterol and were permitted to continue use of all previously prescribed respiratory medications (i.e., long-acting beta-agonists, theophyllines, oral and inhaled steroids, antibiotics, and mucolytics) with the exception of anticholinergics during the observation period; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity.

A significantly smaller proportion of patients in the SPIRIVA group experienced a COPD exacerbation during the six month treatment period compared with placebo (27.8% vs. 32.3%; 5.7% reduction; p=0.037). Likewise, a smaller proportion of patients in the SPIRIVA group were hospitalized for exacerbations compared to the control group, however this difference approached but did not reach statistical significance (7.0% vs. 9.5%; 2.5% reduction, p=0.056). [11,12]

Secondary endpoints evaluating exacerbation and related-hospitalizations support the above findings. SPIRIVA was associated with a significant reduction in the number of exacerbations and number of exacerbation days. In addition, SPIRIVA was associated with a reduction in the number of hospitalizations (p=.047) and a reduction in number of hospitalization days (p=0.019). Similar reductions were seen in the number of antibiotic days (p=0.015) and number of unscheduled visits (p=0.019). Hospitalization days and systemic corticosteroid treatment days for an exacerbation did not statistically differ between the two groups, nor did all-cause hospitalizations or all-cause hospitalization days. The table below reports these data. [11,12]

Secondary Endpoints: Exacerbations and Hospitalizations* [12]

	Spiriva (n=914)	**Placebo (n-=915)**	**Difference**	**p value**
# exacerbations	0.85	1.05	- 0.20	0.031
# exacerbation days	12.6	16.0	- 3.35	0.019
# antibiotic days	8.1	9.8	- 1.71	0.015
# steroid days	6.3	7.4	- 1.15	0.25
# unscheduled visits	0.39	0.49	- 0.11	0.019
# hosp due to exac	0.18	0.25	- 0.08	0.047
#hosp days due to	1.4	1.7	- 0.27	0.054
#all-cause hosp	0.450	0.510	- 0.05	0.68

#all-cause hosp days	3.7	3.5	0.14	0.77

*# per patient year

Furthermore, time to first exacerbation (p=0.028) was significantly prolonged with SPIRIVA. The time to first hospitalization (p=0.055) was prolonged in the SPIRIVA group, although this relationship was of borderline statistical significance. [11,12]

While previous core clinical trials excluded patients using home oxygen, in this trial they are considered an important subgroup as they generally have more severe COPD and have a greater likelihood of a severe exacerbation. Of the home oxygen using patients, 37% had at least one exacerbation and 13% had at least one COPD related hospitalization compared to 27% and 6% for the corresponding events in patients without home oxygen.

e. MISTRAL

The MISTRAL study evaluated the effects of tiotropium on exacerbations of COPD. Using a standard definition and severity classification of exacerbations (somewhat different from the one-year and the six-month core trials), frequency and severity of exacerbations were monitored in a 1-yr, randomized, double-blind, placebo-controlled trial. 1010 COPD patients (mean FEV_1 1.37L, 47.9% pred; age 64.8yrs; 88% men) with a history of at least one exacerbation in the previous year, were randomly assigned to tiotropium 18 µg qd or placebo in 177 centers in France. Results were:

	Tiotropium	Placebo	Reduction	p-value
Mild, moderate and severe exacerbations				
Patients with ≥1 exacerbation (%)	49.9	60.3	-17%	<0.01
Mean no. of exacerations/yr	1.57	2.41	-35%	<0.01
Mean no. of days of exacerbations/yr	21.1	33.3	-37%	<0.01
Moderate to severe exacerbations				
Patients with ≥1 exacerbation (%)	30.6	43.7	-30%	<0.01
Mean no. of exacerbation/yr	1.06	1.64	-35%	<0.01
Mean no. of days of exacerbations/yr	15.1	23.0	-34%	<0.01

Time to first exacerbation was significantly reduced with tiotropium (p<0.001). The significant effect of tiotropium on reduction of exacerbations was independent of the use of inhaled corticosteroids. In patients receiving inhaled corticosteroids (N=615), incidence of exacerbations was significantly reduced by 29% with tiotropium (1.79 vs 2.52 exacerbations/yr, p=0.0014). In those not on inhaled corticosteroids, the frequency of exacerbations was reduced by 44% with tiotropium (1.24 vs 2.23 exacerbations/yr) but did not reach statistical significance due to the smaller group size (N=388). In conclusion, tiotropium significantly reduced the frequency of COPD exacerbations. This effect was also observed in COPD patients treated with inhaled corticosteroids. [13]

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